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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/915,580	07/27/2001	Shinya Uchida	0397-0431P	8191

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EXAMINER	
COOK, LISA V	

ART UNIT	PAPER NUMBER
1641	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/915,580	UCHIDA ET AL.	
	Examiner	Art Unit	
	Lisa V. Cook	1641	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 09 December 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☐ The period for reply expires _____months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☒ A Notice of Appeal was filed on *03 February 2004*. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Attachment*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☐ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: *NONE*.

   Claim(s) objected to: *NONE*.

   Claim(s) rejected: *1-11*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☒ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). *03052004*.

10. ☐ Other: _____

ADVISORY ACTION

Request for Reconsideration

1. Applicant's response to the final office action mailed 4 August 2003 is acknowledged. Applicant request for reconsideration fled therein has been carefully considered.

2. Currently, claims 1-11 are pending and under consideration.

OBJECTIONS WITHDRAWN

Information Disclosure Statement

3. The listing of references in the specification is not a proper information disclosure statement. For example see page 12. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the examiner-on form PTO-892 or the applicant-on form PTO-1449 have cited the references they have not been considered.

Applicants contend that all the references cited in the specification were submitted on the IDS filed 27 July 2001. Accordingly the objection is withdrawn.

4. The information disclosure statement filed 05 March 2004 has met the requirements under *MPEP 609 (d) and (e)*. Accordingly it has been considered After Final.

Priority

5. Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Application No. 2000-226270 filed in JAPAN 7/27/00.

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a translation of the foreign application should be submitted under 37 CFR 1.55 in reply to this action.

Applicants declined the Examiners invitation to incur the expense of providing an unnecessary certified English translation of the priority document at this time. No declaration of interference has been made, accordingly the objection is withdrawn.

REJECTIONS MAINTAINED

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negative by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

I. Claim 1 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamao et al. (US Patent 6,030,845) in view of JP 60047962 - Terumo Corp – Abstract Only.

Yamao et al. disclose an immunoassay method for lysed whole blood. Antibodies in the sample (whole blood) are subjected to agglutination reaction with insoluble carriers or an insoluble particle suspension reagent on to which the antibodies or antigens are immobilized. The agglutination mixture may be lysed with a low osmotic solution, a solution of saponins, freeze/thawing, or by ultrasonication. The resulting agglutination reaction mixture is analyzed for the change in absorbance or in its light scatter by irradiation. See abstract and column 2, lines 9-67.

Yamao et al. do not teach agglutination before the introduction of an erythrocyte-lysing agent (hemolysis).

However, in patent JP 60047962 hemolyzing agents directed to erythrocyte lysing are employed. A whole blood sample is treated with polystyrene latex sensitized with human gamma globulin (to initiate agglutination) and the sensitized latex was mixed with 0.5% Bovine serum albumin and 0.4% saponin (hemolysing agent) to form a reagent for the detection of rheumatoid factor in whole blood. See abstract.

It would have been obvious to one of ordinary skill in the art at the time of the invention to agglutinate before utilizing the lysing agent as taught by Terumo Corp (JP60047962) in the method of Yamao et al. because Terumo Corp (JP60047962) taught that "hemolyzing agents cause hemolysis of erythrocytes which interfere with the agglutination reaction". See abstract. One of ordinary skill in the art at the time the invention was made would have been motivated to agglutinate prior to lysing to eliminate the interference exhibited when the process is reversed.

II. Claims 2 and 3 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamao et al (U.S.Patent #6,030,845) in view of JP 60047962 to Terumo Corp – Abstract Only and in further view of Bester et al. (Analytical Biochemistry, Vol. 223, No.2, pages 299-305, 1994).

Please see Yamao et al. in view of JP 60047962 to Terumo Corp are set forth above.

Yamao et al. in view of JP 60047962 to Terumo Corp differ from the instant invention in not specifically teaching the utility of an erythrocyte-lysing agent (such as sodium dodecyl sulfate) to lyse erythrocytes.

However Bester et al. teach methods of employing and optimizing lysing agents like sodium dodecyl sulfate (SDS). See abstract. Bester et al. further disclose that the use of SDS with fluorescent dyes could be optimized to quantify DNA in cell cultures. See page 299 2nd column 1st paragraph.

It would have been obvious to one of ordinary skill in the art at the time of the invention to employ SDS as a lysing agent to lyse cells as taught by Bester et al. in the method of Yamao et al. in view of JP 60047962 to Terumo Corp because Bester et al. taught that SDS was effective in cell dissolution. See page 299, 2nd column, 1st paragraph. One of ordinary skill in the art at the time the invention was made would have been motivated to incorporate the SDS in cellular analysis to therein take advantage of its known dissociation properties.

III. Claims 4-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamao et al. (U.S.Patent #6,030,845) in view of JP 60047962 to Terumo Corp – Abstract Only and further in view of Kosako (U.S.Patent #5,527,714) and Cohen et al. (U.S.Patent #4,851,329).

Please see Yamao et al. in view of JP 60047962 to Terumo Corp as set forth above.

Yamao et al. in view of JP 60047962 to Terumo Corp fail to particularly teach flow cytometry analysis, particle size, and particle to sample ratios.

However, Kosako disclose a method for determining particle size distributions with respect to an analyte via mediated particle agglutination. The method involves the utility of antigen/antibody reactions to concentrated sensitized insoluble carriers into non-aggregated and aggregated particles of known size.

The analyte is analyzed by an electronic analyzer to detect the quantity and size distribution of concentrated non-aggregated and aggregated insoluble carriers resulting from the antigen/antibody reaction, as well as spurious particles that may be present in the analyte. See column 1 line 65 through column 2 line 9. The calculation with respect to T and M as recited in claim 6 is taught by Kosako (5,527,714) column 4 lines 36-50.

Cohen et al. also disclose a method of determining the concentration of antibody and antigen molecules with high specificity, accuracy, and sensitivity. The process can be used to determine concentration of any substance capable of promoting or inhibiting an agglutination reaction. See abstract. The process is based on the relationship between cluster size of aggregated particles and the intensity of light scatter from the particles as they traverse a beam of focused light. Column 2 lines 62-67. The particle size range from 0.03 up to about 5-10 microns. Column 4, lines 24-26. In the example in column 7 the mixture of particle to sample was taught to be 1:11 (see column 7 lines 54-55).

It would have been obvious to one of ordinary skill in the art at the time of the invention to incorporate the flow analysis teachings of Kosako and Cohen et al. into the method of Yamao et al. in view of JP 60047962 to Terumo Corp because Kosako taught that his method detected small percentages of an analyte with improved sensitivity and decreased sample preparation time. Column 1 lines 30-34. The agglutination process further allowed for spurious particle elimination Column 2 lines 10-16. While, Cohen et al. taught that his method resulted in high intrinsic sensitivity and specificity of the agglutination reaction, improved light scatter detection, while identifying contaminants. Column 6 line 57 through column 7 line 25.

One of ordinary skill in the art at the time the invention was made would have been motivated to measure agglutination in flow cytometry particle analyses to more accurately measure the analyte with various particle parameters thus allowing for increased data sets for consideration and evaluation.

IV. Claims 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Yamao et al. (U.S.Patent #6,030,845) in view of JP 60047962 to Terumo Corp – Abstract Only and further in view of Holmes (U.S. Patent #4,830,969).

Please see Yamao et al. in view of JP 60047962 to Terumo Corp are set forth above.

Yamao et al. in view of JP 60047962 to Terumo Corp differ from the instant invention in not teaching the immune agglutination reaction temperature and time recited in claim 10.

However Holmes disclose a process for the separation of cellular materials. The cellular material is heated in a solution of lysing agent (including surfactants) to agglomerate water-soluble nitrogen containing compounds. See abstract.

In general the temperature is between about 60° and about 105°C., preferably between 80° and 105°C. The time is between about 10 seconds and about 3 minutes. Column 2, lines 54-63. Therein reading on the limitations of claim 10.

It would have been obvious to one of ordinary skill in the art at the time of the invention to utilize the temperature and time ranges taught by Holmes in the method of Yamao et al. in view of JP 60047962 to Terumo Corp because Holmes taught that this process (temp and time) allowed one to separate agglomeration resistant water soluble nitrogen containing cellular organic compounds like nucleic acids and peptides from other cellular materials. Column 2, lines 1-9.

Further the need for isolating plasmids and other nucleic acids has become critical due to the extremely rapid growth of microbiological analysis and genetic engineering. Column 1, lines 56-65.

One of ordinary skill in the art at the time the invention was made would have been motivated to utilize the process taught by Holmes because it was rapid, simple, and inexpensive. Column 1 lines 51-55.

Response to Arguments

7. Applicant contends that the cited references do not teach the instant invention because they teach hemolysis prior to or simultaneously with agglutination. This argument has been carefully considered but not found persuasive for the following reasons:

A. Applicant argues that although the reagent combination is taught by the prior art the instant invention starts with a different material/reagent. Specifically the instant method adds an antibody to the sample then adds a lysing reagent, while the prior art adds the lysing reagent prior to the antibody or in combination with the antibody. This argument was carefully considered but not found persuasive because it has been held that the use of known reagents to produce the results taught by the prior art is obvious. Merely arranging the steps of a known process with out a showing of unexpected result does not read over the prior art teaching.

B. Applicant argues that the claimed sequence of reactants is critical to the practice of the instant invention; however merely reversing the order of the steps in a multi-step process does not impart patentability when no unexpected result is obtained. *Ex parte Rubin* (POBA 1959) 128 USPQ 440.

C. Applicant contends that the prior art does not teach lysis after agglutination. However, the English translation of the complete specification of Japanese Patent Application No. 60-47962 has been provided by Applicant and teaches the use of a hemolytic agent or lysing agent prior to or in combination with the aggregation or agglutination on page 4 section III, 2nd paragraph. The Japanese patent measures the same result as the instant invention (agglutination) further exhibiting results when the lysing agent is added before agglutination or simultaneously with the agglutinating reagent, absent evidence to the contrary the lysing reagent has been shown not to interfere with agglutination and as such could be added at any time during the reaction to achieve the same result.

Further, Yamao et al. (6,030,845) teach that the utility of their hemolytic - lyses reagent not effecting the agglutination reaction. (column 2 line 4). Accordingly the hemolytic step may be performed before or after the agglutination step. No more than routine skill is involved in adjusting the amount of a component of the claimed process to suit a particular starting material (lysing agent or antibody added 1st) in order to achieve the result taught in the prior art. *Exparte Rasmussen* (POBA 1959) 123 USPQ 498.

Applicant contends that Yamao '845 teaches away from the instant method because column 6 lines 5-8 disclose that the surface-active agents (lysing solution) inhibit the agglutination reaction. This argument was carefully considered but not found persuasive because Yamao '845 also teach that the simultaneous addition of the lysing and agglutination reagent provided the expected result (agglutination measurement). In fact, both Yamao et al. and JP60047962 teach the simultaneous addition of both the agglutination reagents and lysing reagent. Although the instant disclosure teaches unexpected results over methods wherein blood samples are first hemolyzed followed by agglutination (Table 1 page 14), it does not show unexpected results when the reagents (agglutination and lyses) are added/conducted simultaneously.

Applicant also argue that the JP '962 patent does not teach the hemolysis of erythrocytes. This argument was carefully considered, but not found persuasive because the patent discloses hemolytic lysing reagents and hemolytic agents breakdown red blood cell or erythrocytes.

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

Therefore it appears that the order of reagent addition or reaction steps are not critical. Absent evidence to the contrary the process of agglutinating prior to lysing is viewed as an obvious modification of the prior art method taught by Yamao et al. in view of JP60047962.

With respect to the 103 rejections cited in items II through IV above, Applicant argues that the rejections must fail since the rejection of claim 1 is overcome. The argument was considered and not found persuasive. Therein the rejections are maintained.

8. For reasons aforementioned, no claims are allowed.

9. **THIS ACTION REMAINS FINAL.**

Remarks

10. Prior art made of record and not relied upon is considered pertinent to the applicant's disclosure:

A. Lehnen (U.S. Patent #5,567,627) teach methods and reagents useful in the simultaneous and discrete analysis of multiple analytes.

B. Terstappen et al. (U.S. Patent #5,646,001) affinity-binding separation and release of one or more selected subset of biological entities from a mixed population thereof.

11. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform to the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The Group 1641 Fax number is (703) 872-9306, which is able to receive transmissions 24 hours/day, 7 days/week.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lisa V. Cook whose telephone number is (571) 272-0816. The examiner can normally be reached on Monday-Friday from 8:00 AM - 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le, can be reached on (571) 272-0823.

Any inquiry of a general nature or relating to the status of this application should be directed to Group TC 1600 whose telephone number is (571) 272-1600.

Lisa V. Cook
Remsen 3C-59
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5/19/04

JAMES HOUSEL 5/19/04
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